

**REMARKS**

Upon entry of the present Reply, claims 8, 14, 16 and 18 are pending in this application. Claim 8 is amended herein. Claims 7, 9, 15 and 17 are cancelled herein, without prejudice. Claims 1-6 and 10-13 were previously cancelled.

Regarding the statement in the Office Action that the claims are not limited to cells commensurate with the evidence presented, Applicants respectfully note that, in addition to the evidence submitted in the Declaration accompanying this Reply to Office Action, Examples 4, 5 and 6 teach that DNA can be efficiently transferred not only into T cells but also into Hela cells and *in vivo* (C57B6 mouse).

In addition, the claims have been amended to specify application of the method to eukaryotic cytoplasm or nucleus.

Thus, Applicants respectfully submit that the scope of the claims is commensurate with the scope of the disclosure.

**Rejections of Claims over Ye et al. in view of Zuckerman**

Claims 7-9 and 14 stand rejected as obvious over Ye et al. in view of Zuckerman. Applicants respectfully traverse this rejection for at least the following reasons.

Applicants respectfully submit that Ye et al. evaluates the effect of the method of delivering protein in a cell by PTD by using a luciferase reporter gene. In particular, Applicants submit that Ye et al. produces expression vectors of chimeric proteins incorporating the transcriptional activator (Gal4DBD-VP16AD) and PTD (Tat or VP22), and tests the ability of the PTD to deliver protein in a cell by the luciferase activity expressed by co-transfecting the chimeric proteins obtained from bacteria in a cell which is already transfected with the Gal4-luciferase reporter vector.

In contrast, Applicants submit that the present invention, as described in claim 8, has two steps which differ significantly from Ye et al.: obtaining a binding complex by combining the [PTD]-[DNA or RNA binding domain (Gal4DBD)] fusion protein with the [target DNA]-[DNA or RNA binding sequence specifically binding to the DNA or RNA

binding domain] recombinant expression vector outside a cell (step iv); and delivering the binding complex into the cell (step v).

In contrast, Ye et al. has a step of binding [PTD-Gal4DBD-VP16AD] and DNA (Gal4 binding site-Luciferase) inside a cell.

Based on the foregoing distinctions, Applicants respectfully submit that the presently claimed invention would not have been obvious over Ye et al. in combination with Zuckerman. Applicants respectfully request reconsideration and withdrawal of the rejections of the claims over this combination.

#### **Declaration of Sang-Kyou Lee**

Applicants submit herewith the Declaration of Dr. Sang-Kyou Lee. In addition, Applicants submit herewith the Curriculum Vitae of Dr. Lee, which clearly shows that Dr. Lee is a person of skill in the art.

The method of the invention described in presently pending claims 8, 14, 16 and 18 shows a significant effect on delivering a biological regulator such as DNA into a cell as shown in the comparative data described in the Declaration submitted herewith.

As stated in the Declaration, lipofectamine is widely used for delivery of naked DNA. However, lipofectamine cannot deliver the naked DNA into suspended cells such as T cells. In contrast, delivery using the method described in claims 8, 14, 16 and 18 can deliver naked DNA regardless of target cell type.

The present inventors have carried out the experiment described in the Declaration to demonstrate the different results obtained by a process in accordance with the present invention as compared to the prior art.

As set forth in the Declaration, pGFP (green fluorescence protein)-GBS (ga14 binding sequence), lipofectamine (Invitrogen) and Mph1-Ga14 were prepared, and primary T (CD3+) cells were extracted from rat spleen tissue. The complexes of lipofectamine-pGFP-GBS (prior art) and Mph1-Ga14-pGFP-GBS (the present invention) were added to a 35 mm Petri dish in which primary T cells ( $2 \times 10^5$ ) were incubated. After adding the complexes, the samples were incubated for 24 hrs and the green fluorescence which was

expressed by the delivered pGFP was detected by FACS analysis. The results are shown in the graphs included in Exhibit A to the Declaration, and the results demonstrate a clear and unexpected distinction between the prior art and the present invention.

Accordingly Applicants respectfully submit that these results clearly demonstrate that the presently claimed invention of claims 8, 14, 16 and 18 would not have been obvious. Therefore, Applicants respectfully request withdrawal of the asserted rejections and allowance of the claims. Notice to such effect is respectfully requested.

### **Conclusion**

For the reasons set forth in the foregoing, Applicants respectfully submit that the present application is in condition for allowance, and an early notice to such effect is respectfully requested.

Should the Examiner consider that a telephone interview would be helpful to facilitate favorable prosecution of the above-identified application, the Examiner is invited to contact the undersigned at the telephone number provided below.

Petition and the fee for a three-month extension and for an RCE is submitted herewith. The assignee of the present application is a small entity, and the fees submitted are for a small entity. If any additional fees are required for the filing of this paper, Applicants request the Commissioner to charge the fees to deposit account #18-0988, Dkt. No. NAMNP0103US.

Respectfully submitted,  
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